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Clinicians' Perspectives on Cure in Adult Patients with Acute Lymphoblastic Leukemia with Minimal Residual Disease: A Delphi Study

Wendy Gidman · Shweta Shah · Lirong Zhang · Jan McKendrick · Ze Cong · David Cohan · Oliver Ottmann

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ABSTRACT

Hematologic complete remission (CR) is achievable for most adults with B cell precursor acute lymphoblastic leukemia (BCP-ALL). However, minimal residual disease (MRD) in patients with hematologic CR is associated with increased risk of relapse, shorter survival, and poorer transplantation outcomes. This study explored the concept of cure in adults with Philadelphia chromosome-negative (Ph⁻) BCP-ALL by MRD status at first hematologic CR (CR1) to inform evaluation of the clinical and

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W. Gidman · L. Zhang · J. McKendrick (✉)
PRMA Consulting Ltd, Fleet, UK
e-mail: jmckendrick@prmaconsulting.com

S. Shah · Z. Cong
Global Health Economics, Amgen Inc., Thousand Oaks, CA, USA

J. McKendrick
Faculty of Health, University of Technology Sydney, Sydney, Australia

D. Cohan
Global Development, Amgen Inc., Thousand Oaks, CA, USA

O. Ottmann
Division of Cancer and Genetics, School of Medicine, Cardiff University, Cardiff, UK

economic benefits of new agents, where the concept of cure is important but long-term data are not available. The study used modified Delphi methodology involving clinicians experienced in the treatment of adult ALL. Participants completed a questionnaire, which was followed by country-specific panel discussions to discuss results and identify consensus on concepts and definitions. Clinicians from France ($n = 4$), Germany ($n = 4$), and the UK ($n = 5$) took part. Participants described cure in terms of the probability of future relapse. Relapse-free survival (RFS) was the preferred outcome measure to describe cure for the three patient groups considered (patients with MRD at CR1; patients who become negative for MRD after further treatment; patients who continue to have MRD). Consensus was reached on definitions of cure: that cure would begin to be considered at 3 years' RFS and/or would be highly likely at 5 years' RFS. Participants agreed that patients with MRD should usually undergo hematopoietic stem cell transplantation to have the best chance of survival; consensus was reached that alternatives are required when transplantation is not an option. Panels agreed that patients who achieve cure have a higher mortality rate and lower health-related quality of life than the general population. This study provides quantitative and qualitative information on the concept of cure in Ph⁻ BCP-ALL in CR by MRD status applicable to interpreting the value of new therapies.

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PLAIN LANGUAGE SUMMARY

Acute lymphoblastic leukemia (ALL) is a blood cancer caused by abnormal white blood cells in the bone marrow. Patients with ALL are given chemotherapy to destroy the abnormal cells, but in some patients a small number of abnormal cells remain that cannot be detected by conventional methods. The risk of disease returning is greater for these patients than for patients without residual abnormal cells.

New therapies are being introduced for ALL that may help patients to achieve cure, but there is no clear agreement on how cure should be defined. To find out, we asked the opinions of specialists to see if they could reach a consensus. As the presence of residual abnormal cells increases the likelihood that ALL will return, we asked these specialists to consider groups of patients with and without these cells. The specialists agreed that:

- The length of time that patients continued without their disease returning was important in deciding whether the disease was likely to be cured.
- Patients (with and without residual abnormal cells) are considered likely to be cured after 3–5 years of their disease not returning.
- Patients with residual abnormal cells should usually undergo stem cell transplantation to have the best chance of survival.
- Patients who are cured have poorer health and a higher risk of dying than people who have not had ALL.

The information gained from this study will help interpret evidence from clinical trials by suggesting which long-term outcomes of

patients treated with new therapies are most meaningful.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a rare hematologic malignancy that shows bimodal incidence, with most cases occurring in children (80%), followed by a gradual increase in incidence after 50 years of age [1, 2]. Approximately three-quarters of adult ALL cases are of B cell lineage, the majority originating from B lymphocyte precursors (BCP-ALL) [3].

For most adults with ALL, front-line chemotherapy will result in hematologic complete remission (CR) (based on morphologic assessment), which is a prerequisite, but by itself not sufficient, for cure. Patients who achieve hematologic CR can potentially harbor leukemic cells in the bone marrow. The presence of leukemic cells that are below the threshold of detection by conventional morphologic methods is referred to as minimal residual disease (MRD).

Large-scale analyses have shown a strong association between the presence of MRD after front-line chemotherapy and poor long-term outcomes, including increased risk of relapse and shorter relapse-free and disease-free survival [4–8]. European clinical guidelines therefore recommend testing patients in first hematologic complete remission (CR1) for MRD for the purpose of risk stratification [9], and this is reflected in national protocols for the treatment of adult ALL. This risk stratification dictates whether immediate (allogeneic) hematopoietic stem cell transplant (HSCT) is indicated for a given patient, because of a higher risk of relapse, or whether that patient should receive additional chemotherapy, because the lower risk of relapse would outweigh the mortality and morbidity associated with HSCT. Nevertheless, the current European guidelines lack deep clarity on the most appropriate use of MRD status and other prognostic factors for clinical decision-making in adults. In addition, the designated MRD status of an individual patient may be influenced by the detection technology and the time point of measurement. Decisions about treatment are

further complicated by the recent approvals of immunotherapies for the treatment of adults with ALL (including blinatumomab, inotuzumab ozogamicin, and chimeric antigen receptor T cell therapy), as it is not yet clear how HSCT should be used in future treatment pathways incorporating these agents.

The concept of cure has been highlighted as particularly important when assessing the value of immunotherapies, for which treatment outcomes suggest that cure may be an increasingly achievable goal [10–12]. The long-term survival of patients who have received a new treatment versus the standard of care (SOC) is frequently critical to quantify potential clinical and economic benefits; however, data over longer time frames are rarely available, necessitating estimation of long-term outcomes using assumptions informed by expert opinion. Specifically, this includes understanding after what time point it may be assumed that patients will continue to survive in the long term, and what will be their long-term health status. This study was initiated to provide such estimates for patients in first hematologic CR in a transparent and methodologically sound manner, in the absence of previously published findings for this patient population.

Given the demonstrable prognostic implications of MRD in patients with BCP-ALL, this study aimed to use MRD status as the basis to explore concepts of cure, with the focus on adults with Philadelphia chromosome-negative (Ph[−]) BCP-ALL. Patients with Ph⁺ BCP-ALL were not considered in this study, as this group represents a minority with its own specific treatment pathways (including the use of tyrosine kinase inhibitors) and a distinctly different prognosis. This study also aimed to understand clinicians' perspectives on the relationship between HSCT and cure, specifically whether HSCT is required for a patient to be considered "cured" in current clinical practice. Further, the study aimed to elicit estimates of the proportion of patients who meet specialists' own definitions of cure in current clinical practice, and to garner understanding of the long-term prognoses of these patients (in terms

of mortality and health-related quality of life, HRQL).

Several of these questions were deemed to be best answered through exploration of expert opinion from clinicians currently treating patients with ALL. Therefore, a consensus approach widely applied in health service research—Delphi methodology—was used for this study.

Representatives from five countries were included in this study: France, Germany, Italy, the UK, and Australia. It was considered valuable to gather country-specific insights into these various concepts, particularly given the differences between national protocols for adult ALL and differences in actual clinical practice. The clinical community treating adults with ALL is small and specialist in nature, such that a panel size of four or five experienced clinicians per country was considered pragmatic and appropriate. The findings based on data collected in France, Germany, and the UK are presented here, as the panels in these countries described similar patterns of practice in treating BCP-ALL and were aligned on definitions of cure. The findings from Italy and Australia were distinct in their definition of cure and will be described in a separate publication.

This report therefore describes the findings of this study for three European countries. In summary, the study aimed to better understand how cure can be defined in adult BCP-ALL for patients in first complete hematological remission and in the context of clinical practice in each country, to inform evaluation of the clinical and economic benefits of emerging agents, specifically immunotherapies.

METHODS

Design

The study used a modified Delphi methodology, which is designed to reach consensus between individuals using questionnaire-based surveys [13]. The study had two phases: phase 1 involved the completion of a Word-based questionnaire; phase 2 involved participation in country-specific virtual panel discussions

(including response gathering and voting). For categorical questions about which consensus for a given country could be evaluated (i.e., non-descriptive questions), consensus was defined by at least 80% of participants being in agreement if five participants were involved (i.e., four out of five participants). When panels involved four participants, consensus was defined as 75% agreement (i.e., three out of four participants). Ethical approval for the study was received from the Human Research Ethics Committee of the University of Technology, Sydney, Australia, and all participants provided informed consent.

Recruitment of Participants

The study aimed to recruit five participants from each of the countries. However, as a result of the limited availability of suitable participants, only four clinicians were recruited in both France and Germany.

Participants were recruited if they met the following inclusion criteria: board-certified or specialized in hematology or hemato-oncology; at least 5 years' experience in this role after completion of training; treats adults with ALL; has seen at least two adults with ALL in the last 12 months, or at least five in the past 5 years; regularly tests patients with ALL for MRD in clinical practice; is able and willing to participate in the Delphi study; and is able to speak and write English as assessed by the research team during recruitment.

The identities of participants were kept confidential during the study, including from the study sponsor, to avoid potential bias.

Data Collection

In phase 1, participants completed Word-based questionnaires sent via email. The questionnaire consisted of categorical, numerical, and open-ended questions and included questions related to background information about the participants and their clinics; definition of cure; cure rates and survival outcomes; and the roles of allogeneic HSCT in achieving cure.

To understand the role of MRD status in the concept of cure, participants were initially asked

to consider patients with Ph–BCP-ALL who were MRD-positive at the first MRD test (defined as the test after country-specific SOC induction therapy, typically used to determine risk of relapse and to establish the treatment plan for a given patient) (population A; Fig. 1). Participants were then asked to consider the concept of cure in two further patient populations: those who are initially MRD-positive at CR1 but who achieve MRD-negative status after subsequent treatment, and those who are MRD-positive at CR1 and remain so after subsequent treatment (populations B and C, respectively; Fig. 1). Participants were asked to define cure based on the general concepts of cure in oncology outlined by Johnson et al. [12], which were made specific to ALL: absence of disease (interpreted as MRD-negative status for patients with ALL at CR1), relapse-free survival (RFS), and overall survival (OS), with stratification for different MRD scenarios as described above. Questions were then asked about mortality risk and HRQL in patients with Ph–BCP-ALL who subsequently are considered to have achieved cure according to the clinician's previously elicited specific definition.

Phase 2 consisted of a series of country-specific panel meetings conducted virtually (through a web conference platform, with audio and screen share capabilities). A summary of the country-specific phase 1 results was provided as input for the panel meetings. For questions about which consensus was reached in phase 1, no further discussion was facilitated in phase 2. When there was no consensus in phase 1, facilitated discussion of the phase 1 results took place, and when appropriate, additional participant responses were collected using an interactive voting system; on occasion, data were recorded manually. The voting involved presenting participants with statements on a topic, derived from phase 1 responses (either repeating questions already asked in the questionnaire after discussion had been completed or new statements based on responses received). The findings of the first panel meeting conducted (in the UK) informed refinement of the statements presented to subsequent panels. Participants were then asked to indicate with which statements they agreed. In some cases, participants could choose more than one statement, while in

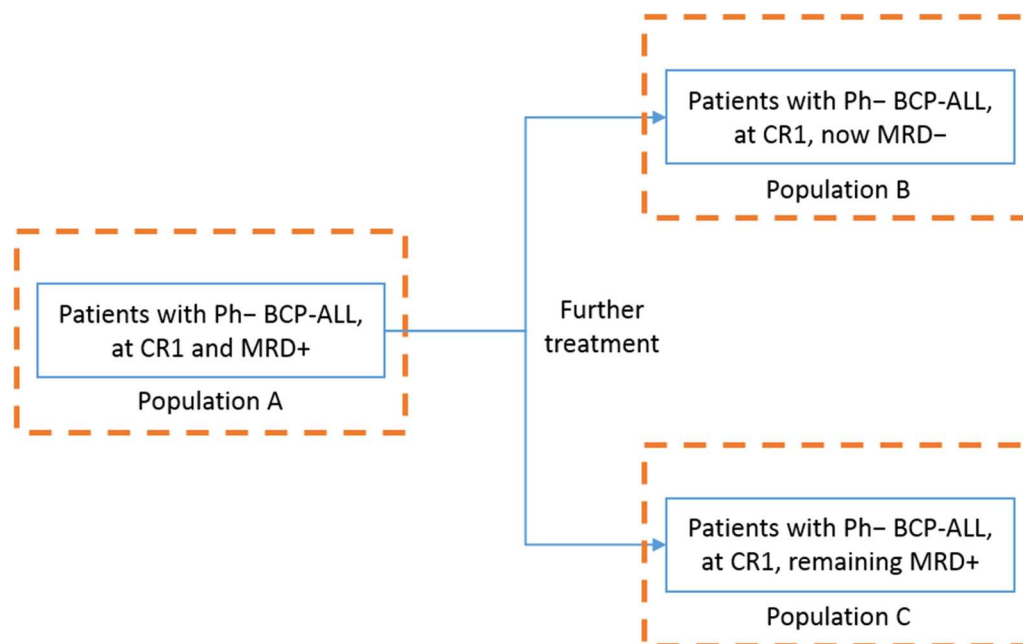


Fig. 1 Patient populations defined for this research. CR1 first complete remission, MRD minimal residual disease, OS overall survival, Ph- BCP-ALL Philadelphia-negative B cell precursor acute lymphocytic leukemia, RFS relapse-free survival

other cases only one answer was permitted. In France, one clinician was unable to attend the panel discussion at the last minute. Therefore, in this case, a one-to-one interview was conducted at a later time: the points raised in the panel were discussed, and the participant was asked to vote on the same statements, without knowledge of the responses from the other participants.

Data Analysis

Data from phases 1 and 2 of the study were entered into Microsoft Excel, anonymized, and analyzed to generate country-specific results. The analyses involved determining frequencies for categorical responses, using standard summary statistics for numerical responses, and identifying common themes from open-ended questions.

RESULTS

Demographics of Panel

A total of 13 clinicians from France ($n = 4$), Germany ($n = 4$), and the UK ($n = 5$) took part

in the study. Nine participants were hematologists and four were hemato-oncologists. The majority of the participants worked in a university hospital ($n = 10$), two were from a designated cancer hospital or specialist oncology center, and one was from a general (urban or community) hospital. All participants were working on clinical teams that conduct HSCT. Overall, participants had a median of 20 years' experience (range 10–30 years) in treating ALL and treated a median of 14 patients (range 8–50) with Ph- BCP-ALL per year.

Definition of Cure

Participants described the potential for cure in terms of probability of relapse, rather than providing a definitive definition (see “Box 1”). They considered this to be a more appropriate way to discuss treatment goals and outcomes in patients with ALL. Importantly, all panels noted that a small minority of patients with ALL experience late relapses, so cure could not be defined with absolute certainty. In patients who are MRD-positive at CR1, participants in all countries described RFS as the preferred

outcome measure for cure. MRD-negative status was described by some participants as an early indicator or predictor of cure, and OS was generally not preferred to RFS (or these measures were considered equivalent given the poor prognosis of ALL after relapse). Similarly, participants agreed that cure should be defined on the basis of RFS in the other patient groups (patients who are MRD-positive but subsequently became MRD-negative, population B, and those who remain MRD-positive, population C).

BOX 1. PARTICIPANT COMMENTS ON THE CONCEPT OF CURE

“Most of the time we call ‘cured’ patients those who are long-term survivors. These patients are mostly MRD-negative, but there is a group of patients who are MRD-positive and still survive. Therefore, I will consider mostly RFS over OS, as patients who are in RFS are also overall survivors.” French clinician

“In my mind, cure is a very strong word and has to be time dependent. I see cure in my patients who remain relapse-free beyond 5 years, and for me there is no surrogate marker to suggest that or earlier time point to make that distinction between RFS and OS.” German clinician

“Here we are talking about probabilities someone is cured and looking at surrogate markers for these probabilities. But there is a distinction between probability and being actually cured; cure is much more than that.” UK clinician

Participants considered the time frames after which patients could be considered to be cured (Table 1). Consensus was reached in France and the UK that for patients who were MRD-positive at the first MRD test, they would begin to consider cure at 3 years’ RFS; in Germany, consensus was reached that cure was highly likely at 5 years’ RFS. Clinicians in each country further agreed that the same definition applies for patients who are MRD-positive but subsequently become MRD-negative

(population B). In all countries, consensus was reached that cure is highly likely at 5 years’ RFS in patients who are MRD-positive and subsequently remain MRD-positive (population C). In the UK, participants also agreed that they start to consider these patients to be cured at 3 years’ RFS. UK panel respondents felt it was more straightforward to define cure for this patient group than for other groups, because research indicates that median time to clinical relapse is short (6–8 months) among such patients.

Participants from France also reached consensus on cure being highly likely if MRD-negative status is sustained for 5 years in patients who are MRD-positive at CR1 but subsequently become MRD-negative (population B). In addition to a definition of cure based on RFS, participants from Germany also reached consensus on a definition based on OS at 5 years, for patients who are MRD-positive but subsequently become MRD-negative (population B).

Likelihood of Cure

Participants were asked what proportion of patients who were MRD-positive at CR1 (population A) are likely to achieve cure with the current local SOC. Participants considered eligibility for HSCT as a critical factor that influences survival. The estimated proportion of patients who are MRD-positive at CR1 and could expect to achieve cure ranged from 30% to 50% in those eligible for HSCT, whereas the cure rate was felt to be considerably lower in those ineligible for HSCT (Table 2).

For patients who were MRD-positive at CR1 but subsequently became MRD-negative or remained MRD-positive (populations B and C, respectively), participants were asked to consider the results of a meta-analysis of event-free survival (EFS) and OS of adults, stratified by MRD status, conducted by Berry et al. [14], which reported EFS of approximately 75% for MRD-negative individuals and approximately 26% for MRD-positive individuals at 3 years. The majority of French participants agreed with

Table 1 Time frame for considering cure, phase 2 results

Patient population	Definition	Percentage of clinicians who agreed with each statement		
		France N=4	Germany N=4	UK N=5
MRD-positive at CR1 (A)	I begin to consider cure when MRD-negative status is sustained for 2 or 3 years ^a	50%	0%	60%
	I begin to consider cure at 3 years' RFS	75%	0%	80%
	Cure is highly likely when MRD-negative status is sustained for 5 years	25%	25%	0%
	Cure is highly likely at 5 years' RFS	50%	100%	60%
	Cure is highly likely at 5 years' OS	0%	50%	0%
MRD-positive but subsequently became MRD-negative (B)	I begin to consider cure when MRD-negative status is sustained for 2–3 years ^b	50%	0%	60%
	I begin to consider cure at 3 years' RFS	75%	0%	80%
	Cure highly likely when MRD-negative status is sustained for 5 years	75%	25%	40%
	Cure is highly likely at 5 years' RFS	50%	100%	80%
	Cure is highly likely at 5 years' OS	25%	75%	20%
MRD-positive and subsequently remained MRD-positive (C)	I begin to consider cure at 3 years' RFS	50%	0%	80%
	Cure is highly likely at 5 years' RFS	75%	100%	80%
	Cure is highly likely at 5 years' OS	25%	50%	0%
	Cure is not possible in these patients	25%	0%	20%

The points of consensus are highlighted in orange. The time point stated was adapted according to the results obtained in phase 1 of the study

CR1 first complete remission, MRD minimal residual disease, OS overall survival, RFS relapse-free survival

^a France, Germany: 2 years, UK: 3 years

^b France, Germany: 2 years, UK: 3 years

the survival outcomes reported in the published meta-analysis for patients who are MRD-positive but subsequently become MRD-negative (population B; Table 2). In the other countries, the majority of participants thought that this patient population would have a lower rate of survival. Consensus was reached among participants from France and the UK that the current

survival outcomes for patients who are MRD-positive and remain MRD-positive after subsequent therapy (population C; Table 2) were at least as poor as those shown in the meta-analysis. German participants either suggested a lower estimate of the proportion of such patients who achieve cure or stated that those

Table 2 Estimates for cure rate, phase 2 results

Patient population	Estimates for cure rate		
	France	Germany	UK
MRD-positive at CR1 and eligible for HSCT	50%	40–50%	30%
MRD-positive at CR1 and ineligible for HSCT	20%	10–20%	Lower than for those eligible for HSCT (not further defined)
MRD-positive but subsequently became MRD-negative	Agreement with the results of the meta-analysis ($\approx 75\%$)	50–60%	30–50%
MRD-positive and subsequently remained MRD-positive	Agreement with the results of the meta-analysis ($\approx 26\%$)	No consensus ^a	Agreement with the results of the meta-analysis ($\approx 26\%$)

CR1 first complete remission, HSCT hematopoietic stem cell transplant, MRD minimal residual disease

^a Two participants stated that these patients cannot be cured, whereas the other two participants estimated a 10–20% cure rate for this patient population

who remained MRD-positive could not be cured.

Necessity of HSCT for Cure

Participants were asked to consider whether patients could be cured without HSCT, and how HSCT is used currently in clinical practice in their respective countries. Results are provided in Table 3 and participants' comments in "Box 2".

BOX 2. PARTICIPANT COMMENTS ON THE NECESSITY OF HSCT FOR CURE

"We do not fully know at the moment, because we have new tools in trials such as immunotherapies, but we do not know whether MRD negativity after immunotherapy has the same prognostic impact as MRD negativity after HSCT." French clinician

"A very small number of patients who are MRD-positive can be cured with conventional chemotherapy, perhaps about 10%. Allograft is better." UK clinician

"There is probably no need for transplantation for these very few patients who became MRD-negative after previously being positive without transplantation." UK clinician

"HSCT is the option which you would offer to patients. Most of the patients will have either matched related or unrelated donor; for those who do not have matched donor, the gap will be closed with offering haplo-identical transplantation, so virtually everyone will have a donor." German clinician

"HSCT is for now the SOC for this group (patients who are MRD-positive at CR1). I hope this changes in the future. For now, if it is possible, I still look for a transplant." French clinician

Participants from all three countries agreed that HSCT is the current SOC for patients who are in CR1 and are MRD-positive (population A). In France, participants also agreed that cure is possible without HSCT in this population; however, in Germany and the UK, consensus was not reached. Clinicians noted in panel discussions that a small proportion of this patient group could achieve cure with chemotherapy alone.

For the other two populations (populations B and C), participants from all three countries agreed that HSCT is not always an option and that alternatives are required. It was noted in the German panel discussion that the use of haplo-identical donors minimized the

Table 3 Requirement for HSCT to achieve cure, phase 2 results

Patient population	Definition	Country		
		France	Germany	UK
MRD-positive at CR1	HSCT is standard of care in this patient group	75%	100%	100%
	HSCT is essential for cure this patient population	25%	50%	0%
	Cure is possible without HSCT in this population	75%	50%	40%
MRD-positive but subsequently became MRD-negative	HSCT is not always a treatment option and alternatives are required	100%	100%	100%
	HSCT is essential to cure this patient population	50%	50%	20%
	Cure is possible without HSCT in this population	50%	50%	60%
MRD-positive and subsequently remained MRD-positive	HSCT is not always a treatment option and alternatives are required	100%	100%	Not asked in the UK
	HSCT is essential to cure this patient population	75%	75%	Not asked in the UK
	Cure is possible without HSCT in this population	25%	25%	Not asked in the UK

The points of consensus are highlighted in orange

CR1 first complete remission, *HSCT* hematopoietic stem cell transplant, *MRD* minimal residual disease

Table 4 Mortality and HRQL in patients who achieve cure, phase 2 results

Patient population	Definition		Country		
			France	Germany	UK
MRD-positive but subsequently achieved cure	Mortality rate higher than in general population	Yes, all patients cured	75%	100%	100%
		Yes, patients cured and who underwent HSCT	100%	75%	100%
	Mortality rate following HSCT	2–3 times higher	50%	25%	20%
		3–4 times higher	50%	25%	80%
		More than 4 times higher	0%	50%	0%
	HRQL	Lower than general population	75%	100%	100%

The points of consensus are highlighted in orange

CR1 first complete remission, *HRQL* health-related quality of life, *HSCT* hematopoietic stem cell transplant, *MRD* minimal residual disease

proportion of patients in their clinical practices who were not able to undergo HSCT because of lack of a donor. Consensus was not reached in

any country as to whether HSCT was essential for cure in those who became MRD-negative. In France and Germany, consensus was reached

that HSCT was essential for cure in those who remained MRD-positive.

Participants in all three countries speculated that in the future, the introduction of immunotherapies could provide the prospect of cure without the need for HSCT; however, they noted that, at present, evidence of the long-term effectiveness of such therapies is lacking.

Impact of Treatment on Mortality

Participants were asked how the mortality rate of patients with Ph⁺ BCP-ALL who were MRD-positive, but subsequently achieved cure, compared with that in the age- and gender-matched general population.

Consensus was reached in all three countries that the mortality rate in patients who achieve cure is higher than that in the age- and gender-matched general population. The phase 1 questionnaire referred to a study by Martin et al. that detailed the long-term mortality risk following HSCT in a US treatment center as being four to nine times higher than that of the general population [15]. In France and the UK, there was consensus that the mortality rate following HSCT was not more than four times higher than in the general population, reflecting improvements in post-transplant surveillance and supportive care since the study by Martin et al. Consensus was not reached in Germany on whether mortality was more or less than four times higher.

Impact of Treatment on HRQL

Participants were asked to consider the HRQL of patients with Ph⁺ BCP-ALL who were MRD-positive but subsequently achieved cure. Results are provided in Table 4 and participants' comments in "Box 3".

BOX 3. PARTICIPANT COMMENTS ON THE IMPACT OF TREATMENT ON HRQL

"Beyond 3 years after transplant, factors contributing to mortality rate are treatment-related; before that, factors are disease-related. Even without a transplant, these patients will suffer from all sort of complications including organ failure, kidney damage, infections, and secondary malignancies." UK clinician

"For sure HRQL will be lower compared with the general population due to psychological problems related to treatment they received, as well as poor social functioning." French clinician

"Long-term HRQL depends more upon the treatment which is given. Patients cured through HSCT would have poorer HRQL than those cured by chemotherapy. HRQL usually improves at later follow-up time points." German clinician

"Some patients have chronic GVHD [graft-versus-host disease] and this affects their utility substantially. Those who do will not approach normal utilities." UK clinician

"It is a question of GVHD mostly... If a patient has been cured without transplant, the HRQL is not very different from the general population." French clinician

"The HRQL increases every year after transplant, for at least 5 years. Of course, patients would not achieve the same quality of life as untreated patients. But it would improve over time." German clinician

Consensus was reached in all three countries that HRQL would be lower in cured patients than in the age- and gender-matched general population. This was stated as primarily being due to chemotherapy- and HSCT-related complications, such as GVHD; the latter was identified by some participants as the critical determinant of the HRQL of patients after transplantation. Other factors that were identified as detrimental to HRQL in those who achieved cure included prolonged time in

hospital, somatic sequelae, psychological problems, cognitive dysfunction, disruption of social activities, and infertility. Several participants commented that HRQL may improve over time in the years after a patient has achieved cure.

DISCUSSION

The concept of cure has become an important element in healthcare decision-making in recent years. Critically, in this disease area, the lack of clarity regarding the definition of cure for adult Ph–BCP-ALL makes it challenging to interpret evidence about the long-term efficacy and relative value of emerging agents. This study was conducted using a Delphi approach to analyze the expert opinions of clinicians currently treating patients with ALL. The findings highlight both areas of commonality among experts from the three countries included, as well as areas where consensus could not be reached.

Our research aligns with other studies [16, 17], indicating that clinicians are hesitant to define patients as definitively “cured” because of the risk of late relapse. Despite this, participants were able to frame the concept of cure as being inversely related to the probability of relapse. Consistent with the results of a prior study using a similar methodology that focused specifically on patients with relapsed and refractory ALL [17], long-term leukemia-free (or in this study, “relapse-free”) survival was seen as key to the concept of cure. Our research complements this previous study; the current study has generated findings on the concept of cure for patients in first hematological remission, and in addition considered the impact of MRD status and provided country-specific findings.

The duration of relapse-free survival after which the potential for cure emerges also aligned among this group of expert panelists: in two of the three country-specific panels, there was consensus that cure could begin to be considered at 3 years’ RFS. The concept of a high likelihood of cure for patients at 5 years’ RFS was also agreed, most notably by all panels for patients in population C (patients who are

MRD-positive and subsequently remain MRD-positive).

When considering the likelihood of cure, participants found it difficult to estimate cure rates for patients with Ph–BCP-ALL, because treatment options are rapidly evolving, the condition is rare, and outcomes vary with age, health status, and eligibility for HSCT. For patients who are MRD-positive, and critically who are eligible for HSCT, consensus among each panel was that cure rates could be expected in the range 30–50%, with considerably lower rates of cure expected among those ineligible for HSCT.

Reflecting the dependence of the probability of cure on eligibility for HSCT, participants pointed out the integral role of HSCT in current clinical practice for patients who are MRD-positive at CR1; they furthermore agreed that allogeneic HSCT cannot be performed in all patients. For patients who are ineligible for HSCT on the basis of age, comorbidities, or availability of a donor, participants agreed that alternative treatments are needed. A number of participants noted that cure is possible in some patients with Ph–BCP-ALL who are MRD-positive, despite not receiving HSCT. There was some speculation about the future role of immunotherapy in patients who have MRD-positive status at CR1. This was discussed as an important option for achieving MRD-negative status, but there was uncertainty regarding the long-term durability of responses to such therapy.

Notably, participants generally agreed that the concept of cure does not imply that “cured” patients are likely to revert to the mortality risk and HRQL expectations of people who have not suffered this disease. However, mortality rates among those considered to be cured from ALL after HSCT were generally felt by panelists to have improved in recent years (two of the three panels agreed that the mortality risk was not more than four times greater than the age- and gender-matched general population). Moreover, some clinicians opined that the impact of BCP-ALL on HRQL varies between individual patients, depending on whether they have long-term complications of treatment, notably

chronic GVHD, and that the detrimental effects of therapy may lessen in subsequent years.

A strength of this study is that the Delphi methodology allows participants to exchange information and discuss their experiences before final responses are captured. Importantly, this method involves collecting both quantitative estimates and qualitative explanations of the rationales behind decisions and opinions. This provides a nuanced understanding of the concepts under consideration and the reasons for agreement or lack thereof.

We also recognize the limitations of this study, particularly with respect to the size of the panels and how representative these are of the country-specific clinician community (i.e., only four or five participants provided their opinions, to represent a country-wide perspective). We do, however, consider these panel sizes to be adequate to provide meaningful results, given the small and specialist nature of the clinical community treating adults with ALL in each country.

CONCLUSIONS

This study offers quantitative and qualitative information on the concept of cure in adults with BCP-ALL in hematologic CR with or without MRD—from the points of view of clinicians in three Western European countries—with the aim of informing evaluation of the clinical and economic benefits of emerging novel therapeutic agents for ALL, specifically immunotherapies. Expert clinicians defined the threshold for reasonable probability of cure for this disease and patient population on the basis of 3–5 years' RFS. The likelihood of cure in patients with MRD was described as dependent on eligibility for HSCT, with clinicians consistently suggesting that alternative therapies are needed for those who are ineligible. Cure was associated with increased mortality risk and negative impacts on HRQL (compared with the general population), critically as a consequence of treatment.

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Compliance with Ethics Guidelines. Ethical approval for the study was received from the Human Research Ethics Committee of the University of Technology, Sydney, Australia. All procedures performed in studies involving human participants were in accordance with the ethical standards of the research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical

standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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